05-22-00 A

Please type a plus sign (+) inside this box → +

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	CRD-850
First Named Inventor or Application Identifier	Gregory A. Kopia et al.
Express Mail Label No.	EL457891230US

APPLICATION ELEMENTS

See MPEP Chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee Transmittal Form *(attached hereto in duplicate)*
2. ☒ Specification [Total Pages 22]
(Preferred arrangement set forth below)
- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R&D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings *(if filed)*
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. ☒ Drawing(s) *(35 USC 113)* [Total Sheets 5]
4. Oath or Declaration
a. ☐ Newly executed (original or copy)
b. ☒ Unexecuted original
c. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional check boxes 5 and 16)
i. ☐ Deletion of Inventor(s)
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation by Reference
(useable if Box 4c is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4c, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
a. ☐ Computer Readable Copy
b. ☐ Paper Copy (identical to computer copy)
c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
14. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)

15. ☒ Other: Abstract

16. ☐ If a CONTINUING APPLICATION, *check appropriate box and supply the requisite information:*
Amend the specification by inserting before the first line: -- This is a ☐ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP) of prior application No.: , filed . --

17. For this divisional application, please cancel original Claims of the prior application before calculating the filing fee.

18. CORRESPONDENCE ADDRESS

☐ Customer Number or Bar Code Label or ☒ Correspondence Address below

Name: Audley A. Ciamporcero, Jr., Esq.
Address: Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003 USA

19. TELEPHONE CONTACT

Please direct all telephone calls or telefaxes to Paul A. Coletti at:
Telephone: (732) 524-2815 Fax: (732) 524-2808

19. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME	Paul A. Coletti	Reg. No. 32,019
SIGNATURE	Paul A. Coletti	
DATE	May 19, 2000	

VIA EXPRESS MAIL NO. EL457891230US
MAILED MAY 19, 2000

05/19/00 JC809 U.S. PTO 09/575480 05/19/00

DRUG COMBINATIONS USEFUL FOR PREVENTION OF RESTENOSIS

Related Application:

This application claims benefit of a provisional application of the same title, S.N. 60/_____, filed May 12, 2000.

Field of the Invention:

This invention describes the delivery of different drug combinations, either systemically or locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention given either systemically or locally also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease related mortality, resulting in 500,000-600,000 deaths annually. Percutaneous transluminal coronary angioplasty (PTCA) to open the obstructed artery was performed in over 550,000 patients in the U.S. and 945,000+ patients worldwide in 1996 (Lemaitre et al., 1996). A major limitation of this technique is the problem of post-PTCA closure of the vessel, both immediately after PTCA (acute occlusion) and in the long term (restenosis): 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. Additionally,

restenosis is a significant problem in patients undergoing saphenous vein bypass graft. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus.

Restenosis after angioplasty is a more gradual process and involves initial formation of a subcritical thrombosis with release from adherent platelets of cell derived growth factors with subsequent proliferation of intimal smooth muscle cells and local infiltration of inflammatory cells contributing to vascular hyperplasia. It is important to note that multiple processes, among those including thrombosis, cell proliferation, cell migration and inflammation each seem to contribute to the restenotic process.

In the U.S., a 30 - 50% restenosis rate translates to 120,000 - 200,000 U.S. patients at risk from restenosis. If only 80% of such patients elect repeat angioplasty (with the remaining 20% electing coronary artery bypass graft) is added to the cost of coronary artery bypass graft for the remaining 20%, the total cost for restenosis easily reaches into billions of dollars. Thus, successful prevention of restenosis could result not only in significant therapeutic benefit but also in significant health care savings.

While the exact mechanism for restenosis is still uncertain, the general aspects of the restenosis process have been identified:

1) In the normal arterial wall, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day). SMC in vessel wall exists in a 'contractile' phenotype

characterized by 80-90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state (Campbell and Campbell, 1985).

2) Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), thrombin, etc., released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., bFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within 1-2 days post-injury and peaks at 2 days in the media, declining thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

3) Daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and begin to secrete significant amounts of extracellular matrix proteins. Proliferation, migration and inflammation continue until the damaged luminal endothelial layer regenerates at which time proliferation slows within the intima, usually within 7-14 days postinjury.

The further increase in intimal thickening that occurs over the next 3-6 months is due primarily to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu *et al.*, 1989).

4) Simultaneous with local proliferation and migration, inflammatory cells adhere to the site of vascular injury. Within 3 – 7 days post injury, luminal adherent cells decline due to migration of inflammatory to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least 30 days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed antiproliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A.W. and Karnovsky M., Nature, 265: 25-26, 1977; Guyton, J.R. et al., Circ. Res., 46: 625-634, 1980; Clowes, A.W. and Clowes, M.M., Lab. Invest. 52: 611-616, 1985; Clowes, A.W. and Clowes, M.M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J.W. et al., Circulation 80: II-66, 1989, taxol (Sollott, S.J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J.S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C.F. et al., Am. J. Cardiol. 17(Suppl. B):

132B-136B, 1991), cyclosporin A (Jonasson, L. et. al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G.A.A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G.M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M.W. et al., Circulation 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G.K. and Holm, J., Circulation 84: 1266-1272, 1991), rapamycin (Marx, S.O. et al., Circ. Res. 76: 412-417, 1995), steroids (Colburn, M.D. et al., J. Vasc. Surg. 15: 510-518, 1992), see also Berk, B.C. et al., J. Am. Coll. Cardiol. 17: 111B-117B 1991, ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M.W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Antiproliferative action on SMC *in vitro* has been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of SMC inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, unlike animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anticoagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang *et al.*, 1991; Popma *et al.*, 1991). Additionally, the 7E3 humanized monoclonal antibody fragment to the platelet GP IIb/IIIa receptor is still under study but has not shown promising results for

the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and antiproliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang *et al.*, 1991; Popma *et al.*, 1991).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements or cholesterol lowering agents has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993; Serruys, P.W. *et al.*, 1993). Recent observations suggest that the antilipid/antioxident agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probucol is presently not approved for use in the United States and a 30-day pretreatment period would preclude its use in emergency angioplasty. Additionally, application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have US Federal Regulatory Agency (FDA) approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven useful in partially preventing restenosis. Stents, are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after PTCA, by increasing minimal lumen diameter and reducing, (but not eliminating,) the incidence of restenosis at 6 months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Heparin coating also appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Post-angioplasty restenosis is a multifactorial process that involves numerous interactive mechanisms. This means that effective prevention of restenosis may not be feasible with agents possessing a single mechanism of action; positive therapeutic results may be best achieved through application of several agents with differing therapeutic targets. Thus, potential therapeutic benefit could be found with the co-delivery of agents with different mechanisms of action targeting different components of the restenosis process.

SUMMARY OF THE INVENTION

The current invention comprises an approach to solving the clinical problem of restenosis, which involves the administration of drug combinations, either locally or systemically. One example of such a combination would be the addition of the antiinflammatory corticosteroid, dexamethasone, with an antiproliferative agent such as cladribine, rapamycin, vincristine, taxol, or a nitric oxide donor. Such combination therapies might result in a better therapeutic effect (less proliferation as well as less inflammation, a stimulus for proliferation) than would occur with either agent alone. Such agents could be administered systemically in their respective therapeutic doses, or, alternatively, could be bound to the surface of a stent by means of incorporation within either a biodegradable or biostable polymeric coating. Alternatively, these agents could be incorporated into a stent constructed with a grooved reservoir. Thus, delivery of a stent containing both an antiproliferative agent and an antiinflammatory agent to a coronary artery injured during the process of angioplasty would provide the added therapeutic benefit of 1) limiting the degree of local smooth muscle cell proliferation, 2) reducing a stimulus for proliferation, i.e., inflammation, and thus enhance the restenosis-limiting action of the stent.

In other embodiments of the inventions, growth factor or cytokine signal transduction inhibitor, such as the ras inhibitor, R115777, or a tyrosine kinase inhibitor, such as tyrphostin, might be combined with an antiproliferative agent such as taxol, vincristine or rapamycin so that proliferation of SMC could be inhibited by different mechanisms. Alternatively, an antiproliferative agent such as taxol, vincristine or rapamycin could be combined with an inhibitor of extracellular matrix synthesis such as halofuginone. In the above cases, agents

acting by different mechanisms could act synergistically to reduce SMC proliferation and vascular hyperplasia. This invention is also intended to cover other combinations of two or more such drug agents. As mentioned above, such agents could be administered systemically, delivered locally *via* drug delivery catheter, or formulated for delivery from the surface of a stent, or given as a combination of systemic and local therapy.

DETAILED DESCRIPTION OF THE DRAWINGS:

The invention will be better understood in connection with the following figures in which:

Figures 1 and 1a are top views and section views of a stent containing reservoirs as described in the present invention;

Figures 2a and 2b are similar views of an alternate embodiment of the stent with open ends;

Figures 3a and 3b are further alternate figures of a device containing a grooved reservoir;

Figure 4 is a layout view of a device containing a reservoir as in Figure 3; and

Figures 5 and 6 are a graph of the performance characteristics of stents coated according to this invention.

DETAILED DESCRIPTION OF THE INVENTION

Multiple Drug Therapy combined with a Stent

As stated previously, implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, a combination of agents, which prevent inflammation and proliferation, or prevents proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis. In this regard, a stent in conjunction with systemic treatment with the drug combinations suggested above or local delivery of such drug combinations is an attractive treatment. Either systemic or local delivery of multiple drugs from a stent has the following advantages:

1. Prevention of vessel recoil and remodeling through the scaffolding action of the stent;
2. Prevention of multiple components of neointimal hyperplasia, the vascular response to injury

Local administration of drug combinations to stented coronary arteries might have additional therapeutic benefit:

1) higher tissue concentrations would be achievable than would occur with systemic administration;
2) reduced systemic toxicity; and
3) single treatment/ease of administration

An additional benefit of combination drug therapy may be to reduce the dose of each of the therapeutic components and thus limiting their toxicity, while still achieving a reduction in restenosis. Combination therapy is therefore a means of improving the therapeutic ratio (efficacy/toxicity) of an antirestenosis agent.

As seen in the accompanying Figures 1-4, it is possible to modify currently manufactured stents in order to provide adequate drug delivery. As seen in Figures 1a, 2a and 3a, any stent strut 10, 20, 30 can be modified to have a certain reservoir 11, 21, 31. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. Figure 4 shows a stent 40 with a reservoir 45 created at the apex of a flexible connector. Of course, this reservoir 45 is intended to be useful to deliver any drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents. Processes for coating such stents are described, for instance, in Serial Nos. 09/061,568, filed 16 Apr 1998, and 09/512,432 filed 25 Feb 2000, both of which are assigned to a common assignee and are incorporated herein by reference.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must

be kept at a size of about 0.1 mm to about 1 mm depth, and 7 mm to 15 mm length, or enough to hold at least a therapeutic amount of the drug. Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

Example 1

To assess the ability of a drug combination to prevent cell proliferation, human smooth muscle cells (Clonetics, Walkersville, MD) were seeded at a density of 10,000 cells/well) into each well of 24-well plates and cultured in growth medium containing heparin, EGF (epidermal growth factor), FGF fibroblast growth factor) and serum. After 24 hours, the growth medium was changed and fresh medium containing various concentrations of test agents (0.01 - 10 mcg/mL) were added to triplicate wells. Medium was replaced with fresh medium (plus test agents) after 3 days. On day five, cells were detached by trypsin/EDTA and counted using a hemacytometer. Cell viability was assessed by trypan blue exclusion.

Table 1 provides the percent of control growth of the various tested concentrations of the antiinflammatory agent, dexamethasone, on human smooth muscle cells, either in the absence or presence of 2 concentrations of the antiproliferative/antiimmune agent, rapamcyin. Dexamethasone produced a concentration-related decrease in the proliferation of smooth muscle cells in this model system. The IC_{50} value (concentration required to produce a reduction in proliferation to 50% of the control cell count) for the inhibition of smooth muscle cells with dexamethasone alone estimated from Table 1 is 5 μg/mL. Addition of 0.2 μg/mL of rapamycin to the incubation media was found to reduce the IC_{50} estimate of dexamethasone to 0.05

μg/mL. A greater added concentration of rapamycin (2 μg/mL) further reduced the IC_{50} estimate for dexamethasone to less than 0.01 μg/mL.

Thus, as the rapamycin concentration was increased in the incubation media, less dexamethasone was required to produce a 50% inhibition of cell growth. Since the amounts of rapamycin employed did not achieve a 50% inhibition of cell growth, Table 1 demonstrates that concentrations of both rapamycin or dexamethasone below their respective IC_{50} amounts may combine to produce an effect on cell growth greater than either agent individually. Such a drug combination may be therapeutically useful for inhibition of the intimal smooth muscle cell proliferation that accompanies stent implantation. While efficacy could be maintained at these lower doses, toxicities associated with each of these agents might be ameliorated.

TABLE 1. Inhibition of human vascular smooth muscle cell proliferation with dexamethasone or dexamethasone + rapamycin.

	Concentration of Dexamethasone (μg/ml)									
	0	0.01	0.05	0.1	0.5	1	5	10	50	100
% of Control Growth										
Rapamycin 0 ug/ml	100.0	-	-	75.2	76.5	72.2	50.0	36.1	18.3	11.7
Standard Deviation	4.2			0.8	16.3	9.3	7.6	5.9	6.0	1.3
Rapamycin 0.2 ug/ml	85.7	63.4	57.6	49.7	48.9	48.2	41.2	31.1	31.2	29.0
Standard Deviation	6.6	3.2	2.1	4.6	2.2	1.7	3.0	2.7	1.0	1.8
Rapamycin 1 ug/ml	67.4	48.3	45.1	38.1	39.2	37.8	33.9	25.8	20.7	18.5
Standard Deviation	2.6	3.3	13.3	9.5	4.4	4.5	3.1	8.1	6.4	3.7

The following examples are used to demonstrate the various configurations of medicated stent coatings containing one or more drugs. These are summarized in Table 2.

Table 2: Coating configurations used to demonstrate controlled release of rapamycin and dexamethasone from a stent

	Drug Content		
Sample I.D	Rap[a]	Dex[b]	Coating Configuration
50/50	82μg	82μg	Drugs are co-mixed with polymer. Total coating wt.: 548μg
0/100	0μg	100μg	Drugs are co-mixed with polymer. Total coating wt.: 641μg
100/0	150μg	0μg	Drugs are co-mixed with polymer. Total coating wt.: 500μg
67/33	103	51	Drugs are co-mixed with polymer. Total coating wt.: 513μg
33/67	53	107	Drugs are co-mixed with polymer. Total coating wt.: 534μg
33/67-3X[c]	182μg	363μg	Drugs are mixed with polymer. Total coating wt.: 1817μg
50/50-OLD[d]	77μg	80μg	Base coat: Rapamycin mixed with polymer. Overcoat: Dexamethasone mixed with polymer. Total coating wt.: 520 μg
50/50-OLR[e]	79μg	81μg	Base coat: Dexamethasone mixed with polymer. Overcoat: Rapamycin mixed with polymer. Total coating wt.: 536 μg
50/50-TC[f]	100 μg	100 μg	Base coat: Drugs are mixed with polymer blend Barrier coat: 158 μg polybutyl methacrylate. Total coating wt.: 811 μg
0/100-TC[f]	0 μg	196 μg	Base coat: Drugs are mixed with polymer blend Barrier coat: 168 μg polybutyl methacrylate. Total coating wt.: 839 μg

a: Rapamycin; b: Dexamethasone; c: 3 time coating thickness; d: Dexamethasone overlayer; e: Rapamycin overlayer; f: Top coated

Example 2

This example describes the preparation of a base coating that contains rapamycin

Stents were coated with Parylene C™ using a vapor deposition method provided by the manufacturer of the parylene-coating instrument (SCS Madison, Wisconsin). The stent is weighed and then mounted for coating. While the stent is rotating a solution of 1.75mg/ml Poly (ethylene-covinyl acetate)(PEVA), 1.75mg/ml polybutyl methacrylate, and 1.5mg/ml rapamycin dissolved in tetrahydrofuran is sprayed onto it. The coated stent is removed from the spray and allowed to air-dry. After a final weighing the amount of coating on the stent is determined.

Example 3

This example describes the preparation of a base coating that contains dexamethasone

Stents were coated with Parylene C™ using a vapor deposition method provided by the manufacturer of the parylene-coating instrument (SCS Madison, Wisconsin). The stent is weighed and then mounted for coating. While the stent is rotating a solution of 1.75mg/ml Poly (ethylene-*co*-vinyl acetate)(PEVA), 1.75 mg/ml polybutyl methacrylate, and 1.5 mg/ml dexamethasone dissolved in tetrahydrofuran is sprayed onto it. The coated stent is removed from the spray and allowed to air-dry. After a final weighing the amount of coating on the stent is determined.

Example 4

This example describes the preparation of a base coating that contains rapamycin and dexamethasone

Stents were coated with Parylene C™ using a vapor deposition method provided by the manufacturer of the parylene-coating instrument (SCS Madison, Wisconsin). The stent is weighed and then mounted for coating. While the stent is rotating a solution of 1.75 mg/ml Poly (ethylene-co-vinyl acetate)(PEVA), 1.75 mg/ml polybutyl methacrylate, 0.75 mg/ml rapamycin and 0.75 mg/ml dexamethasone dissolved in tetrahydrofuran is sprayed onto it. The coated stent is removed from the spray and allowed to air-dry. After a final weighing the amount of coating on the stent is determined.

Example 5

This example describes a stent coating that consists of a base coat containing rapamycin and dexamethasone and a drug-free barrier overcoat

A stent is coated as in Example 4. After the coating is thoroughly dried a solution of 2.5 mg/ml polybutyl methacrylate dissolved in tetrahydrofuran is sprayed onto it. It is then air-dried for a final overcoat weight of 150 μg.

Example 6

This example describes a stent coating, which consists of a base containing rapamycin and an overlayer with dexamethasone

A stent is coated as in Example 2. A solution of 1.75 mg/ml Poly (ethylene-*co*-vinyl acetate)(PEVA), 1.75 mg/ml polybutyl methacrylate, and 1.5 mg/ml dexamethasone dissolved in tetrahydrofuran is sprayed onto it. The coated stent is removed from the spray and allowed to air-dry. The final weight of each layer is typically 250 μg for a total coating weight of 500μg.

Example 7

This example describes a stent coating, which consists of a base containing dexamethasone and an overlayer with rapamycin

A stent is coated as in Example 3. A solution of 1.75 mg/ml Poly (ethylene-*co*-vinyl acetate)(PEVA), 1.75 mg/ml polybutyl methacrylate, and 1.5 mg/ml rapamycin dissolved in tetrahydrofuran is sprayed onto it. The coated stent is removed from the spray and allowed to air-dry. The final weight of each layer is typically 250 μg for a total coating weight of 500μg.

The following examples describe the method and results for testing the *in vitro* release of rapamycin and dexamethasone from coated stent.

Example 8

This example describes the method for performing the *in vitro* release of rapamycin and dexamethasone from coated stent.

Each stent was placed in a 2.5mL of release medium (aqueous ethanol, 25 percent by volume at room temperature) contained in a 13 X 100 mm culture tube with a screw cap. The tube was shaken in a water bath (INNOVA™ 3100,

New Brunswick Scientific) at 200 rpm while maintaining ambient conditions. After a given time interval (ranging from 15 minutes to one day) the tubes were removed from the shaker and the respective stents carefully transferred to a fresh 2.5 ml Aliquot of release medium. The new tube was placed on the shaker and agitation resumed. A sample was removed from the aliquot, which had previously contained the stent and placed in a HPLC vial for determination of the rapamycin content and dexamethasone, by HPLC.

Example 9

This example describes the method for analyzing the release medium for rapamycin.

The HPLC system used to analyze the samples was a Waters Alliance with a PDA 996. This system is equipped with a photodiode array detector. 20μL of each sample was withdrawn and analyzed on a C_{18} –reverse phase column (Waters Symmetry™ Column: 4.6mm X 100mm RP_{18}, 3.5 μm with a matching guard column) using a mobile phase consisting of acetonitrile/methanol/water (38:34:28 v/v) delivered at a flow rate of 1.2 mL/min. The column was maintained at 60°C through the analysis. Under these analytical conditions rapamycin had a retention time of 4.75 ± 0.1 minutes. The concentration was determined from a standard curve of concentration versus response (area-under the curve) generated from rapamycin standards in the range of from 50ng/mL to 50μg/mL.

The results from testing the coated stents described above are shown in Figure 5.

Example 10

This example describes the method for analyzing the release medium for dexamethasone.

The HPLC system used to analyze the samples was a Shimadzu Class-VP Chromatography Laboratory System. This system is equipped with a photodiode array detector. 20μL of each sample was withdrawn and analyzed on a C_{18} – reverse phase column (Waters Symmetry™ Column: 4.6mm X 100mm RP_{18} 3.5 μ). An isocratic mobile phase consisting of methanol/water (55:45 v/v) delivered at a flow rate of 0.8 mL/min. was used for the first 6.5 mins of analysis followed by 100% methanol for 2 minutes; the latter was to ensure removal of rapamycin which is retained on the column. The column was maintained at 25°C throughout the analysis. Under these analytical conditions dexamthasone had a retention time of 5.9 ± 0.1 minutes. The concentration was determined from a standard curve of concentration versus response (area-under the curve) generated from dexamethasone standards in the range of from 40ng/mL to 4.0μg/mL.

The results from testing the coated stents described above are shown in Figure 6.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention, which is to be realized from the attached claims and their equivalents.

WHAT IS CLAIMED IS:

1. A process for the treatment for restenosis comprising the intravascular infusion or delivery by release from the surface of a stent of combinations of at least two drugs to a patient in therapeutic dosage amounts.

2. The method of claim 1 wherein the combination of agents employed includes an anti-inflammatory agent and an antiproliferative agent.

3. The method of claim 2 wherein the anti-inflammatory agent is dexamethasone and the anti-proliferative agent is taken from the group of rapamycin, taxol, or vincristine.

4. The method of claim 1 wherein the combination of agents employed includes a growth factor or cytokine signal transduction inhibitor and an anti-proliferative agent.

5. The method of claim 4 wherein the signal transduction inhibitor is the ras inhibitor, R115777, and the anti-proliferative agent is taken from the group consisting of rapamycin, taxol, or vincristine.

6. The method of claim 1 wherin the combination of agents employed include a tyrosine kinase inhibitor and an anti-proliferative agent.

7. The method of claim 6 wherin the tyrosine kinase inhibitor is tyrphostin and the antiproliferative agent is taken from the group consisting of rapamycin, taxol, vincristine.

8. The method of claim 1 wherein the combination of agents employed includes an inhibitor of extracellular matrix synthesis and an antiproliferative agent.

9. The method of claim 8 wherein the anti-proliferative agent is taken from the group of rapamycin, taxol, or vincristine.

10. The method of claims 4 wherein the signal transduction inhibitor, the tyrosine kinase inhibitor or the extracellular matrix inhibitor is administered in combination with an anti-inflammatory inhibitor.

11. The method of claim 10 wherin the anti-inflammatory agent is dexamthasone.

12. In combination:

a catheter for the delivery of drugs to a blood vessel lumen of a patient; and

a therapeutic dosage amount of the combination of rapamycin and dexamethasone coated to or delivered through said catheter.

13. In combination:

a stent for the delivery of drugs to a lumen of a patient; and

a therapeutic dosage amount of rapamycin and dexamethasone coated to said stent.

14. A stent comprising:

a plurality of struts, said struts expansible within the lumen of the body, and at least one of said struts containing a reservoir therein; and

a therapeutic amount of rapamycin and dexamethasone coated to said stent.

15. The method of claim 8 wherein said exhibitor is halofuginone.

FIG. 1

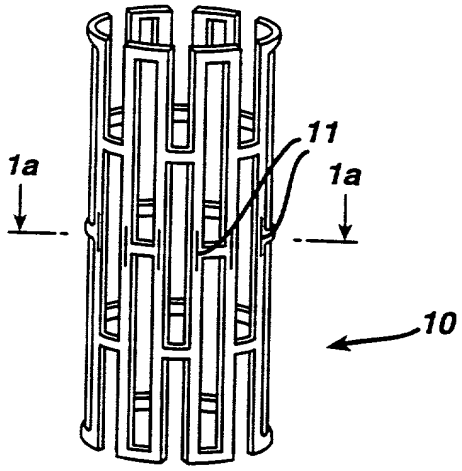


FIG. 1a

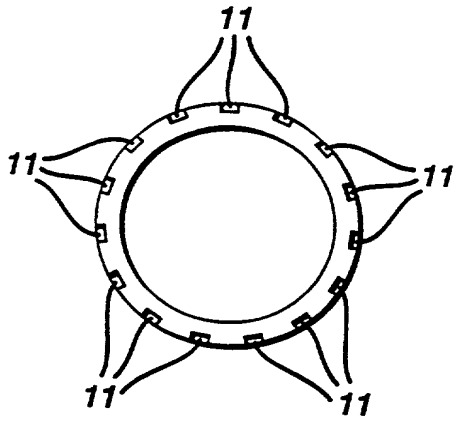


FIG. 2a

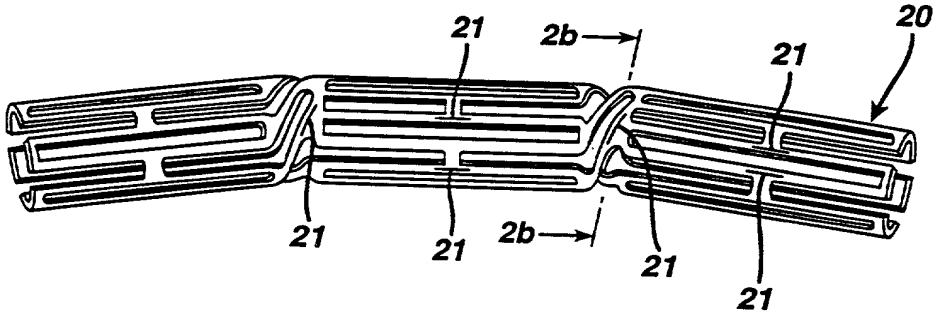


FIG. 2b

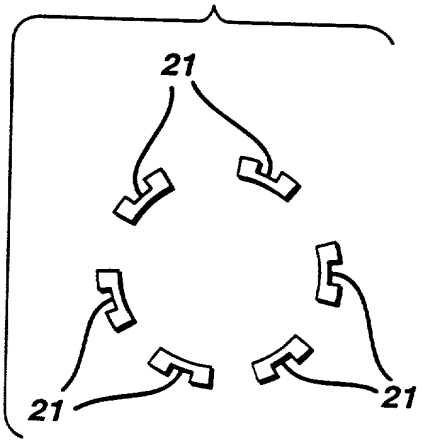


FIG. 3a

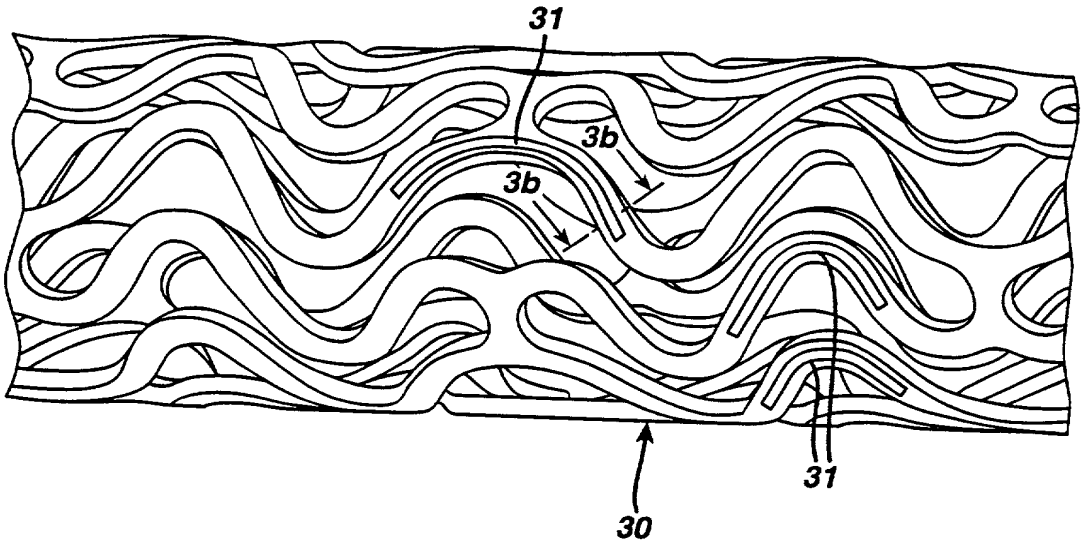


FIG. 3b

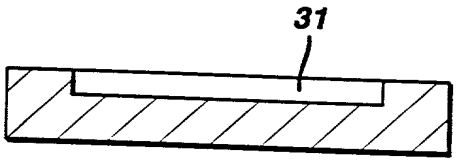


FIG. 4

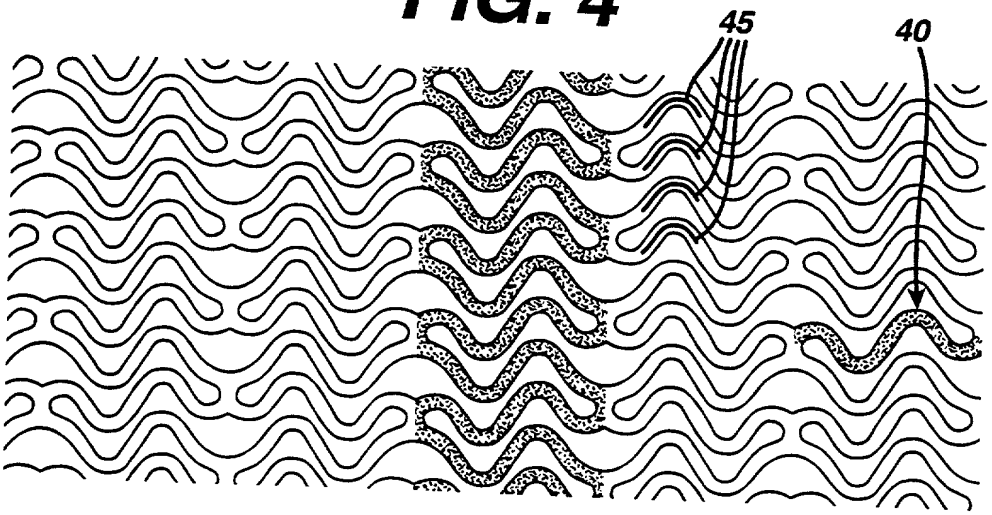


Figure 5

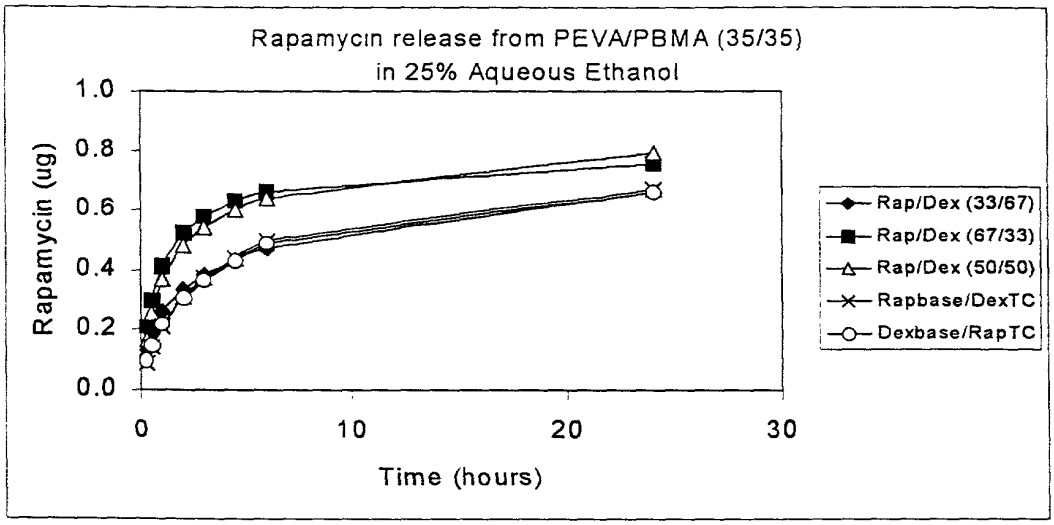


Figure 6

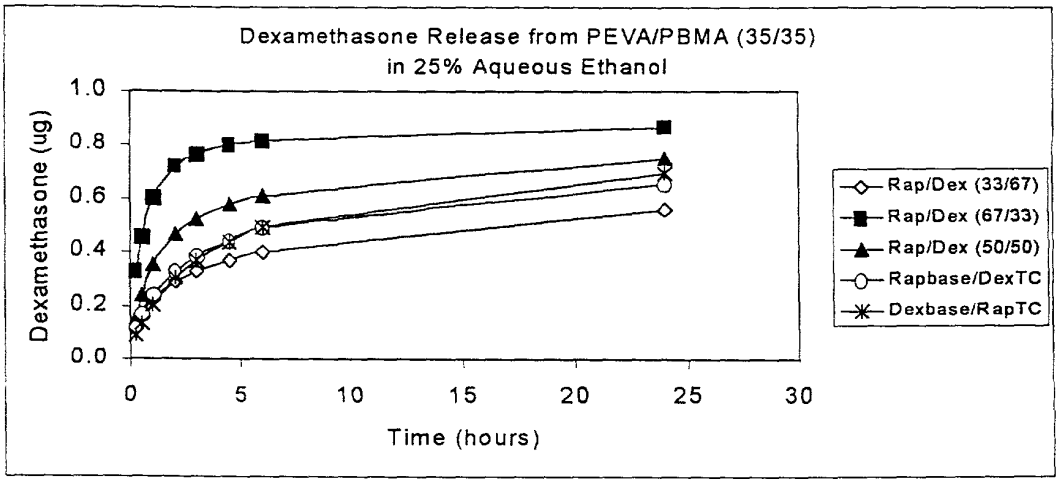


Figure 7

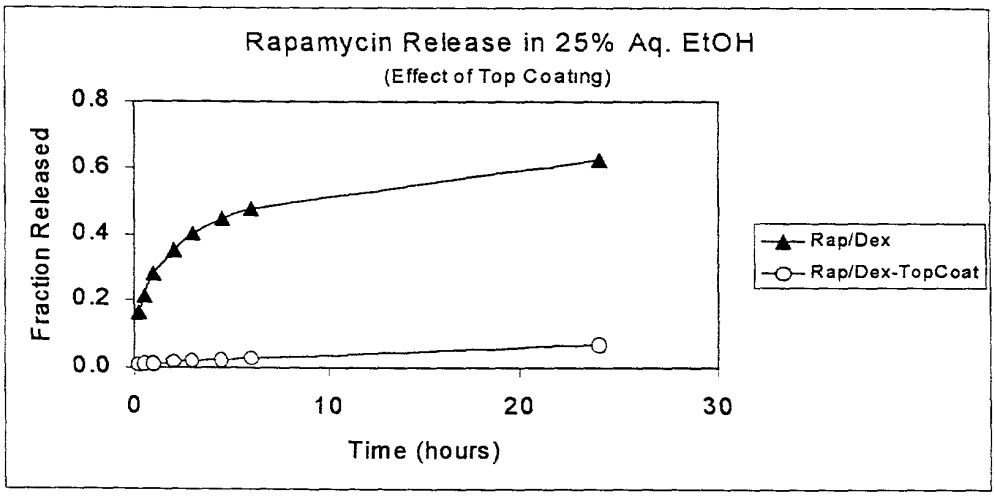


Figure 8

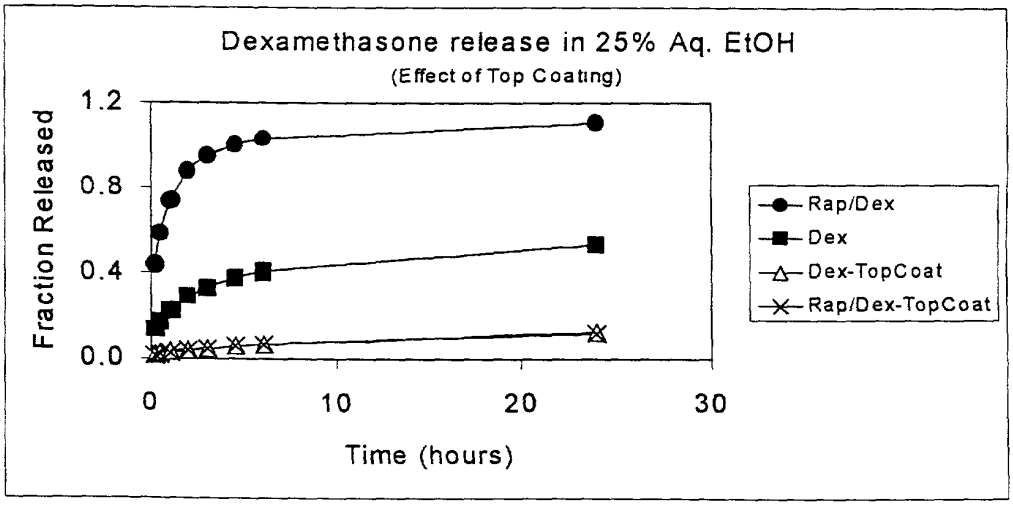
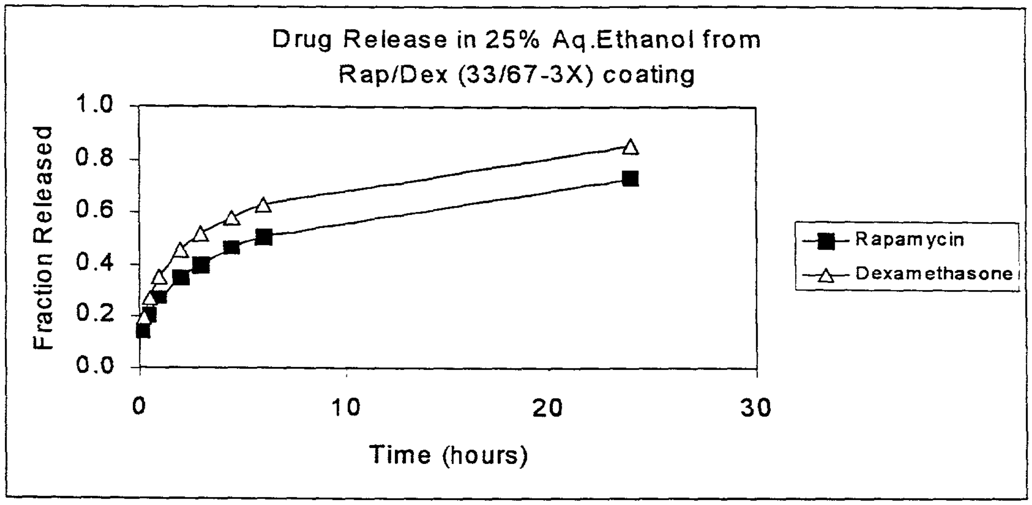


Figure 9


Drug Release in 25% Aq.Ethanol from
Rap/Dex (33/67-3X) coating
1.0
0.8
0.6
0.4
0.2
0.0
Fraction Released
0
10
20
30
Time (hours)
Rapamycin
Dexamethasone

DOCKET NO. CRD-850

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

DRUG COMBINATIONS USEFUL FOR PREVENTION OF RESTENOSIS,

the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____.
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

VIA EXPRESS MAIL NO. EL457891230US
MAILED MAY 19, 2000

Prior Foreign Application(s):

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Not yet assigned (Application Number) — May 12, 2000 (Filing Date)

(Application Number) — (Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No. — Filing Date — Status

Application Serial No. — Filing Date — Status

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith as well as to file equivalent patent applications in countries foreign to the United States including the filing of international patent applications in accordance with the Patent Cooperation Treaty: Audley A. Ciamporcero, Jr. (Reg. #26,051), Steven P. Berman (Reg. #24,772), Andrea L. Colby (Reg. #30,194), Michael Stark (Reg. #32,495), and Paul A. Coletti (Reg. #32,019) One Johnson & Johnson Plaza, New Brunswick, NJ 08933.

Address all telephone calls to Paul A. Coletti at telephone no. (732) 524-2815.

Address all telephone calls to Paul A. Coletti at telephone no. (732) 524-2815.

Address all correspondence to Audley A. Ciamporcero, Jr., One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor's Signature: _____

Full Name of Sole or First Inventor: Gregory A. Kopia

Date: _____

Citizenship: U.S.A.
Residence: 58 Longfield Drive, Neshanic, NJ 08853
Post Office Address: Same as above

Inventor's Signature: _____

Full Name of Second Joint Inventor, If Any: Gerald H. Llanos

Date: _____

Citizenship: Trinidadian
Residence: 1514 Megan Circle, Stewartsville, NJ 08886
Post Office Address: Same as above

Inventor's Signature: _____

Full Name of Third Joint Inventor, If Any: Robert Falotico

Date: _____

Citizenship: U.S.A.
Residence: 40 Black Horse Run, Belle Mead, NJ 08502
Post Office Address: Same as above

(Supply similar information and signature for fourth and subsequent joint inventors.)